IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Confirmation No. 6122
KONIECZNA et al.	Atty. Ref.: 37-86
Serial No. 10/564,148	T.C. / Art Unit: 1618
Filed: November 9, 2006	Examiner: J.M. Vu

FOR: PHARMACEUTICAL FORMULATION COMPRISING LEVOTHYROXINE SODIUM

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APPEAL BRIEF UNDER 37 CFR § 41.37

Monday, December 13, 2010

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this Brief to appeal the Examiner's final rejection as set forth in his Office Action mailed May 11, 2010 (the "final Office Action"). The fee required under 37 CFR § 41.20(b)(2) is submitted herewith.

The Notice of Appeal was filed on October 12, 2010. Thus, this Brief is timely filed because the Patent and Trademark Office (PTO) was closed on December 12, 2010.

Reversal of the Examiner's rejection of claims 18-19 by the Board of Patent Appeals and Interferences (the "Board") is respectfully requested.

I. REAL PARTY IN INTEREST

The assignee, Aspen Global Incorporated, holds all rights in this application, as well as the invention disclosed and claimed therein, by chain of title from the inventors. An assignment from the inventors to Glaxo Group Limited was recorded on February 20, 2006 in the PTO starting at reel 017196, frame 0361. An assignment from Glaxo Group Limited to Aspen Global Incorporated was then recorded on April 14, 2010 in the PTO starting at reel 024256, frame 0557.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the assignee, and the undersigned do not know of any prior or pending appeal, interference, or judicial proceeding which is related to, directly affects or is directly affected by, or has a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 18 and 19 stand rejected. They are at issue in this appeal, and listed in the Claims Appendix below. Claims 1-17 and 20-34 were canceled without prejudice or disclaimer. Cancellation of claim 21 moots the Examiner's objection to the specification, albeit this was not acknowledged in his Advisory Action of October 28, 2010.

IV. STATUS OF AMENDMENTS

A first Amendment was submitted under 37 CFR § 1.116 on August 11, 2010. But the Examiner stated in his Advisory Action mailed August 19, 2010 that this amendment would not be entered.

A second Amendment was submitted under 37 CFR § 1.116 on October 12, 2010. The Examiner stated in his Advisory Action mailed October 28, 2010 that this amendment would be entered. Entry of the amendment moots the Examiner's rejections except for the Section 103(a) rejection argued below.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention of the claims involved in this appeal is directed to a pharmaceutical formulation of levothyroxine sodium. Levothyroxine is a synthetic form of thyroxine (T4), which is a hormone produced by the thyroid gland. A brand name is SYNTHROID.

Independent claim 18 is directed to a pharmaceutical formulation in unit dose form, which comprises: 0.0425-0.0575 mg levothyroxine sodium, 50-60 mg micro-crystalline cellulose which has a mean particle size of less than 125 µm, 12-17 mg pre-gelatinized starch which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, 2-3 mg talc, 1-2 mg colloidal anhydrous silica, and 0.5-1.0 mg magnesium stearate. It is supported by page 1, lines 21-23, and page 4, lines 25 and 29-31, of the specification. Note that "50 µg tablet" at page 4, line 29, of the specification is a nominative amount because the tablet actually contains from 0.0425 to 0.0575 mg levothyroxine sodium (see page 4, line 29, of the specification). Pregelatinized starch is produced by applying mechanical pressure to moistened starch in order to rupture some or all of its starch granules and subsequent drying according to page 2, lines 32-33, of the specification.

Independent claim 19 is directed to a pharmaceutical formulation in unit dose form, which comprises: 0.085-0.115 mg levothyroxine sodium, 100-120 mg micro-

crystalline cellulose which has a mean particle size of less than 125 µm, 24-34 mg pre-gelatinized starch which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, 4-6 mg talc, 2-4 mg colloidal anhydrous silica, and 1-2 mg magnesium stearate. It is supported by page 1, lines 21-23, and page 4, lines 25 and 31-34, of the specification. Note that "100 µg tablet" at page 4, line 31, of the specification is a nominative amount because the tablet actually contains from 0.085 to 0.115 mg levothyroxine sodium (see page 4, lines 31-32, of the specification). Pregelatinized starch is produced by applying mechanical pressure to moistened starch in order to rupture some or all of its starch granules and subsequent drying according to page 2, lines 32-33, of the specification.

Therefore, Appellants' claimed invention is clearly supported by the specification.

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Under 35 U.S.C. 103(a), was it proper to reject claims 18-19 as allegedly unpatentable over Mitra et al. (US 5,955,105) as evidenced by *Handbook of Pharmaceutical Excipients, 5th Ed.* (pp. 134, 725 and 731-732) and the Material Safety Data Sheet for L-Thyroxine, sodium salt in view of *European Pharmacopoeia* (pg. 1438) and Franz et al. (US 2003/0032675)?

VII. ARGUMENTS

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d

1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 18-19 were rejected under Section 103(a) as allegedly unpatentable over Mitra et al. (U.S. Patent 5,955,105; cited as MITRA below) as evidenced by *Handbook of Pharmaceutical Excipients, 5th Ed.* (pp. 134, 725 and 731-732; cited as HANDBOOK below) and a Material Safety Data Sheet (L-Thyroxine, sodium salt; cited as MSDS below) in view of *European Pharmacopoeia* (pg. 1438; cited as PHARMACOPOEIA

below) and Franz et al. (U.S. Application 2003/0032675; cited as FRANZ below). Appellants traverse for the following reasons.

Appellants' Claimed Invention Is MORE Than the Predictable Use of Prior Art Elements

Claims 18-19 are directed to pharmaceutical formulations in unit dose form, which contain specific amounts of numerous components. Both claims require microcrystalline cellulose having a mean particle size of less than 125 μm. Appellants teach in their specification (Example 2) that this limitation confers the advantage of stabilizing their claimed formulations in (B) on pages 7 and 9, where the effect of microcrystalline cellulose particles size on levothyroxine sodium tablets was analyzed:

> The data shows (sic) that a higher levothyroxine sodium content is maintained and the total impurities are lower when microcrystalline cellulose with a mean particle size of 50 μm or 100 μm compared to 180 μm is used in the levothyroxine sodium formulation"

(page 7, lines 33-35, of the specification). Therefore, the limitation requiring the microcrystalline cellulose to have a mean particle size of less than 125 μm results in the claimed invention possessing at least the following unexpected advantages: (1) maintaining higher levothyroxine sodium content and (2) lowering the total impurities for the claimed pharmaceutical formulations. These advantages were not taught or suggested in the documents cited by the Examiner, and no evidence was presented by him that such would have been obvious from the prior art.

MITRA disclosed stabilized pharmaceutical preparations containing levothyroxine sodium. Stabilization was achieved using a water-soluble glucose polymer (e.g., maltodextrins at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as partially soluble or insoluble glucose polymer, and starch as water-soluble glucose polymer. But MITRA

is silent on any advantage of requiring the microcrystalline cellulose to have a mean particle size of less than 125 μm.

Appellants' claimed invention requires microcrystalline cellulose having a mean particle size of less than 125 μm, which was demonstrated to have certain advantages. These advantages of maintaining a higher levothyroxine sodium content and lowering the total impurities were not taught or suggested in the prior art, nor would they have been obvious to one of ordinary skill in the art with a reasonable expectation of success. Further, optimization of mean particle size to increase stability of a levothyroxine formulation was not taught or made obvious by the evidence of record.

Appellants' data in their specification show that a mean particle size of less than 125 μm is critical for stabilizing their claimed pharmaceutical formulation. It is not the expected outcome of routine optimization, and there is no evidence of record that any relationship between mean particle size and stability would have been obvious from the prior art at the time the claimed invention was made.

The failure of MITRA (as evidenced by HANDBOOK and MSDS) to disclose the advantages of Appellants' claimed invention is not remedied by the Examiner's attempt to combine its disclosure with PHARMACOPOEIA and FRANZ. The claimed invention differs from the disclosures cited by the Examiner because claims 18-19 require the microcrystalline cellulose to have a mean particle size of less than 125 μm. PHARMACOPOEIA is irrelevant to microcrystalline cellulose and its mean particle size. FRANZ discloses formulations containing microcrystalline cellulose but, like MITRA, the cited application is silent on any relationship between mean particle size and stability. For example, "Sifting segregation can occur with a mean particle size in the 50 micron

range and can become a dominant segregation mechanism if the mean particle size is above 100 microns" (paragraph [0033]) does not make obvious a mean particle size of less than 125 µm for microcrystalline cellulose.

If a proposed modification would render a prior art invention inoperable for its intended purpose, then the cited prior art effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Here, since segregation of components in a composition is an undesirable characteristic, the disclosure by FRANZ teaches away from the mean particle sizes of 50 µm and 100 µm that were successfully used in Appellants' Example 2. Thus, one of ordinary skill in the art would not have combined disclosures by MITRA and FRANZ.

Further experiments have been performed that were not in Appellants' specification. They evaluate the effects of changing the carrier on stability. A triturate composition of 2.5% w/w levothyroxine sodium in the carrier is selected. Microcrystalline cellulose of various mean particle sizes are evaluated for their suitability as carriers. These data confirm the results shown in Example 2 of Appellants' specification.

Triturates samples are prepared and stored under conditions of 60°C/ambient humidity and 40°C/75% RH for 14 days. The samples are assessed for stability (assay of levothyroxine sodium) and content uniformity of active ingredient (sampled in earlier fixed places). All content uniformity results and stability results are summarized in the following Tables 1 to 7.

Table 1. Batch 010201RB – carrier Cellulose Microcrystalline grade 101

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.46 (98.4)	2.38	2.38
2	2.39 (95.6)	2.39	2.33
3	2.41 (96.4)		
4	2.41 (96.4)		
5	2.40 (96.0)		
6	2.42 (96.8)		
Mean	**2.42 (96.8)**	**2.38 (98.5)**	**2.35 (97.2)**
RSD (%)	**1.0**		

Table 2. Batch 050401RB – carrier Cellulose Microcrystalline grade 101

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.55 (102.0)	2.35	2.35
2	2.47 (98.8)	2.39	2.39
3	2.46 (98.4)		
4	2.44 (97.6)		
5	2.43 (97.2)		
6	2.47 (98.8)		
Mean	**2.47 (98.8)**	**2.37 (95.9)**	**2.37 (95.9)**
RSD (%)	**1.66**		

Table 3. Batch 030401RB – carrier Cellulose Microcrystalline grade 102

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.68 (107.2)	2.46	2.38
2	2.52 (100.8)	2.48	2.42
3	2.52 (100.8)		
4	2.52 (100.8)		
5	2.52 (100.8)		
6	2.56 (102.4)		
Mean	**2.55 (102.0)**	**2.47 (96.7)**	**2.40 (94.2)**
RSD (%)	**2.56**		

Table 4. Batch 040401RB – carrier Cellulose Microcrystalline grade 102

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.60 (104.0)	2.52	2.41
2	2.59 (103.6)	2.48	2.40
3	2.55 (102.0)		
4	2.56 (102.4)		
5	2.62 (104.8)		
6	2.58 (103.2)		
Mean	**2.58 (103.2)**	**2.50 (96.9)**	**2.40 (93.2)**
RSD (%)	**0.98**		

Table 5. Batch 010701RB – carrier Cellulose Microcrystalline grade 103

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.49 (99.6)	2.38	2.27
2	2.36 (94.4)	2.36	2.31
3	2.45 (98.0)		
4	2.48 (99.2)		
5	2.50 (100.0)		
6	2.47 (98.8)		
Mean	**2.46 (98.4)**	**2.37 (96.3)**	**2.29 (93.1)**
RSD (%)	**2.05**		

Table 6. Batch 010401RB – carrier Cellulose Microcrystalline grade 200

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.70 (108.0)	2.26	2.33
2	2.75 (110.0)	2.26	2.23
3	2.63 (105.2)		
4	2.63 (105.2)		
5	2.65 (106.0)		
6	2.61 (104.4)		
Mean	**2.66 (106.4)**	**2.26 (84.9)**	**2.28 (85.7)**
RSD (%)	**1.95**		

Table 7. Batch 020401RB – carrier Cellulose Microcrystalline grade 200

Sample	Levothyroxine sodium content in % (% of declaration value)	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH	Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity
1	2.56 (102.4)	2.29	2.22
2	2.41 (96.4)	2.36	2.13
3	2.45 (98.0)		
4	2.64 (105.6)		
5	2.52 (100.8)		
6	2.51 (100.4)		
Mean	**2.51 (100.4)**	**2.33 (92.5)**	**2.18 (86.5)**
RSD (%)	**3.27**		

Note microcrystalline cellulose Grades 101, 102 and 103 have a mean particle size of 50-100 µm while microcrystalline cellulose Grade 200 has a mean particle size of 180 µm. The above results reinforce the improved stability of formulations containing microcrystalline cellulose having a mean particle size of less than 125 µm.

One of ordinary skill starting from a prior art formulation would not have found it obvious to limit the mean particle size of the microcrystalline cellulose and would not have a reasonable expectation that this change would provide the surprising result that the modified formulation maintains a higher levothyroxine sodium content and lowers the total impurities.

In summary, the cited documents fail to make obvious Appellants' claimed pharmaceutical formulations. In particular, no evidence was presented in the final Office Action that one of ordinary skill in the art would have limited the mean particle size of

microcrystalline cellulose with a reasonable expectation that the formulations' stability would be improved. Therefore, Appellants' claimed invention would not have been obvious from the cited documents.

Appellants' Pregelatinized Starch Is NOT Functionally Equivalent To Unmodified Starch

Claims 18-19 also require that their pharmaceutical formulations contain pre-gelatinized that is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying. As noted above, MITRA disclosed stabilized pharmaceutical preparations containing levothyroxine sodium. Stabilization was achieved using a water-soluble glucose polymer (e.g., maltodextrins at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as partially soluble or insoluble glucose polymer, and starch as water-soluble glucose polymer. But contrary to previous assertions by the Examiner, pregelatinized starch as present in Appellants' claimed invention is not functionally equivalent to MITRA's water-soluble starch. One of ordinary skill in the art would not have found it obvious to substitute them interchangeably because there is no evidence of record (including FRANZ) that 'pre-gelatinised starch' and 'starch' are functional equivalents. Further, there is no reasonable expectation of substituting one for the other in a formulation containing levothyroxine without a change in function.

Both HANDBOOK and PHARMACOPOEIA, which were cited by the Examiner, list the entities 'starch, pregelatinized' and 'starch' (unmodified) separately because they are universally recognized in the art as distinct excipients with very different properties and functionalities. It is not possible to merely substitute starch for pregelatinized starch

in a pharmaceutical formulation without changing the characteristics of the formulation and, as such, they are not mere functional equivalents.

The requirement of Appellants' claimed formulations to include pregelatinized starch provides them with different solubility characteristics as compared to other formulations containing water-soluble, unmodified starch. Additionally, pregelatinized starch has a number of other different chemical and physical properties as compared to unmodified starch. Specifically, pregelatinized starch possesses enhanced flow and compression characteristics as compared to unmodified starch: pregelatinized starch granules occur as irregular chunks or thin plates, whereas unmodified starch occurs as a powder comprising very small spherical or ovoid granules. Thus, in contrast to the Examiner's assertion made to justify the obviousness rejection, 'pregelatinized starch' and 'starch' are clearly not functional equivalents.

Furthermore, the compatibility with lubricants of pregelatinized starch and unmodified starch is different and altering the excipient may require a change in the choice of lubricant. Replacing the starch in the formulation of MITRA's Example 10, which has 0.5% magnesium sterate, with pregelatinized starch would be expected to have a not insubstantial effect on tablet strength and dissolution properties. Thus, the magnesium sterate lubricant may need to be replaced by stearic acid or the level of magnesium sterate reduced to compensate for that change (see HANDBOOK at page 731). Thus, pregelatinized starch is not merely an alternative for unmodified starch having some properties that may be used interchangeably since one of ordinary skill in the art making the Examiner's proposed substitution would have reasonably expected to make other changes in the formulation (e.g., choice and/or amount lubricant).

The failure of MITRA (as evidenced by HANDBOOK and MSDS) to disclose the claimed invention is not remedied by the Examiner's attempt to modify its disclosure with PHARMACOPOEIA and FRANZ. There is nothing in FRANZ that would have made it obvious to one of ordinary skill in the art to replace starch in an existing formulation with pregelatinized starch, nor was there any evidence that such a replacement would lead to an advantage. On the contrary, FRANZ clearly sets out that the formulations to which it relates are within the parameters that are described in MITRA's Example 10 (see paragraph [0026]) and, thus, the changes required by the Examiner's combination would not have been obvious from the cited documents.

In the context of the cited documents as a whole, claim 6 of FRANZ would not be interpreted by one of ordinary skill in the art as disclosing that starch in the formulations described in MITRA should or could be replaced with pregelatinized starch. On reading FRANZ, one of ordinary skill in the art seeking guidance concerning the exact composition of a levotroxin-containing formulation would have turned to MITRA. Given that MITRA is concerned with advantageous levotroxin-containing formulations, whereas FRANZ is silent on the merits of various pharmaceutical excipients, one of ordinary skill in the art would take MITRA as being authoritative on the excipient blend, as FRANZ acknowledged itself. Therefore, one of ordinary skill in the art would either ignore the nature of the excipients listed in FRANZ's claim 6 or, in the unlikely event they are considered relevant, would modify FRANZ's formulation to conform to MITRA's formulation instead of the reverse because FRANZ's claim 6 was outside the parameters set out in MITRA.

Here, there is no evidence of record that 'pregelatinized starch' and 'starch' are functional equivalents. If they were functionally equivalent, starch could be substituted for pregelatinized starch in claims 18-19 without affecting the advantages of Appellants' formulations. But the Examiner did not establish a reasonable expectation that his proposed substitution would have no effect on stabilization. Therefore, Appellants' claimed invention would not have been obvious from the cited documents.

Documents Cited By Examiner Do NOT Teach All Limitations of the Claimed Invention

Finally, claims 18-19 contain additional requirements for specific amounts of levothyroxine sodium, microcrystalline cellulose having a mean particle size of less than 125 µm, pregelatinized starch produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, talc, colloidal anhydrous silica, and magnesium stearate. This is an independent basis for patentability from the differences argued above: (1) the stabilizing effect of microcrystalline cellulose having a mean particle size of less than 125 µm and (2) pregelatinized starch not being functionally equivalent to unmodified starch.

There are no findings in the final Office Action that would be relevant to these specific amounts. In this respect, only MITRA disclosed specific preparation containing levothyroxine sodium but they appear to be only the following unit dose forms: 25 µg, 100 mg and 300 mg of the active ingredient. No unit dose form of the required 0.0425-0.0575 mg ("50 µg tablet") or 0.085-0.115 mg ("100 µg tablet") levothyroxine sodium was disclosed, let alone any disclosure of the specific amounts of components of the formulations described in claims 18 and 19. Further, there is no teaching in any of the cited documents that would lead the person of ordinary skill in the art to prepare unit

dosage forms having the specific amounts of components required by the claims. Therefore, claims 18-19 would not have been obvious from MITRA in view of PHARMACOPOEIA and FRANZ.

Appellants urge the Board to reverse the Section 103 rejection because their claimed invention would not have been obvious to one of ordinary skill in the art.

Conclusion

For the reasons discussed above, the Examiner's rejections are improper and they should be reversed by the Board. Appellants submit that the present claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

VIII. CLAIMS APPENDIX

Claims 1-17 (canceled)

18. (previously presented) A pharmaceutical formulation in unit dose form which is a "50 µg tablet" of active ingredient comprising: 0.0425-0.0575 mg levothyroxine sodium, 50-60 mg microcrystalline cellulose which has a mean particle size of less than 125 µm, 12-17 mg pregelatinised starch which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, 2-3 mg talc, 1-2 mg colloidal anhydrous silica, and 0.5-1.0 mg magnesium stearate.

19. (previously presented) A pharmaceutical formulation in unit dose form which is a "100 µg tablet" of active ingredient comprising 0.085-0.115 mg levothyroxine sodium, 100-120 mg microcrystalline cellulose which has a mean particle size of less than 125 µm, 24-34 mg pregelatinised starch which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, 4-6 mg talc, 2-4 mg colloidal anhydrous silica, and 1-2 mg magnesium stearate.

Claims 20-34 (canceled)

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.